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(57) Abstract

A composition, particularly adapted for oral administration, comprising a benzimidazole, except omeprazole, preferably pantoprazole, and a method for preparing it are provided, the composition being exempt of alkaline-reaction compounds and comprising a core constituted of nuclei and said benzimidazole, the nuclei and benzimidazole being compressed together, an intermediate layer and an enteric layer.

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NOVEL COMPOSITION CONTAINING AN ACID-LABILE BENZIMIDAZOLE AND PROCESS FOR ITS PREPARATION

BACKGROUND OF THE INVENTION

This present invention relates to a novel composition containing an acid-labile benzimidazole, and to its preparation. This novel composition is perfectly suitable for oral administration. The invention also relates to a process for preparing this composition.

Many substances, of pharmaceutical value, that are labile in an acid medium have been described in the literature. The substances disclosed in the following patents can be given by way of example: EP 244 380, US-P-4 045 563, EP-0 005 129, BE-898 880, GB-2 141 429, EP-0 146 370, GB-2 082 580, EP-A-0 173 664, EP-A-0 080 602, EP- 0127 763, EP-0 134 400, EP-0 130 729, EP-0 150 586, DE-34 15971, GB-2 082 580, SE-A-8504048-3 and US-4 182 766. On the other hand, omeprazole, which is of the family of benzimidazoles, corresponding to an anti-ulcer substance, used conventionally for decreasing gastrointestinal acid secretion, is well known and has been notably discussed in Swedish patent application 78.04231 filed on April 14, 1978, as well as in numerous other patents. Pantoprazole and lansoprazole which both correspond to anti-ulcer substances of the omeprazole family, are notably discussed in US-P-4,758,579 and in US-P-4,628,098 respectively.

Chemical substances that are easily destroyed in an acid medium (which is expressed herein by the term "acid-labile" and meaning chemical substances that are labile in an acid medium), such as benzimidazoles and, in particular, omeprazole, lansoprazole and pantoprazole, create a special problem for formulators when it is required to provide a pharmaceutical form designed for oral administration. The product does indeed come into contact with the stomach content, which is a highly acid medium, leading to breakdown of these chemical substances.

In order to avoid contact between the substances and the acid gastric juice following oral administration of the

substance, a pharmaceutical formulation is conventionally used, such as a capsule or tablet which contains a core (tablet, microgranule, pellet, etc.....) containing the acid-labile active substance and an outer layer that surrounds this core and which consists of a gastro-resistant composition that is entero-soluble. Generally, the coating agent is a compound that is particularly insoluble in an acid medium, but which is soluble in a neutral or alkaline medium.

For substances that are highly labile in an acid medium but which are more stable in a neutral or alkaline medium, such as omeprazole, pantoprazole and lansoprazole, it is necessary to add an inert substance to the composition, which leads to an alkaline reaction aimed at improving stability of the active substance during manufacture thereof, and during storage of the pharmaceutical form.

Several prior art documents describe such compositions that are suitable for oral administration of acid-labile substances.

EP-0,244,380 discloses pharmaceutical formulations that are suitable for oral administration of acid-labile substances. It is stated that these acid-labile substances intended for oral administration must be protected by an enteric coating, but conventional enteric coatings of an acid nature are not suitable for this purpose. If one were indeed to cover acid-labile substances which such coatings, the substance would be rapidly decomposed due to direct or indirect contact with the coating, which manifests itself by a change of color and a decrease in the active substance content with the passage of time. The solution proposed in that patent corresponds to formulations consisting of: (a) a core in the form of small particles, i.e. pellets or compressed powder, containing the active substance along with an alkaline reacting compound, (b) one or several inert intermediate layers containing excipients for tablets which are soluble, and which rapidly disintegrate in water, water-soluble film-forming polymer compounds optionally containing alkaline compounds acting as a pH buffer between the core having an alkaline reaction and the outer layer, and (c) an

outer layer consisting of an enteric composition. It is also stated that, in order to improve storage stability, the cores containing the active substance should also contain constituents having an alkaline reaction, and that the water that enters by diffusion, or the gastric juice, will dissolve part of the core close to the enteric coating, forming an alkaline solution at this level inside the coated form for administration. This patent claims pharmaceutical formulations containing acid-labile active substances of formula I with the notable exception of omeprazole.

EP-A-0,247,983 which is related to pharmaceutical formulations that are suitable for oral administration of acid-labile substances adopts the general principles developed in EP-A-0,244,380 in order to more particularly apply them to the case of omeprazole. The main claim in that application thus covers the association of omeprazole with an auxiliary alkaline-reacting substance..

United States patent 4,786,505 discloses novel stable preparations containing omeprazole intended for oral administration, their preparation and a method for treating gastrointestinal sicknesses using these novel preparations. These oral pharmaceutical preparations comprise: (a) a core comprising omeprazole and an alkaline reacting compound, an alkaline salt of omeprazole and an alkaline-reacting compound or an alkaline salt of omeprazole alone; (b) at least one inert intermediate layer that is water-soluble or rapidly disintegrates in water; and (c) an external layer comprising an enteric coating.

EP-A-0,519,365 discloses pharmaceutical formulations that are suitable for oral administration of pantoprazole, comprising an acid-labile substance . In order to improve stability of pantoprazole formulations, this document discloses the use of the active substance in a salt form. The pharmaceutical formulations disclosed comprise: (a) a core containing the active principle in a salt form, (b) at least one water-soluble intermediate layer and (c) an outer layer corresponding to an enteric coating. It is stated that the use of a salt form in the core enables an alkaline environment to be created that protects the active

substance. If the salt form does not have a sufficient effect on the pH, it is necessary to add a constituent that has an alkaline reaction to the core.

EP-A-0,519,144 discloses a novel process for producing a stable preparation containing omeprazole, intended for oral administration. This document notably discloses a process for preparing pellets containing omeprazole in which a core constituted of inert substances is covered by the active substance in finely divided form and dispersed in an aqueous dispersion buffered to a pH of 7.0, after which an enteric coating is applied, the finished product being placed inside a capsule.

United States patent 5,232,706 discloses novel stable pharmaceutical preparations containing omeprazole, intended for oral administration. The pharmaceutical compositions disclosed comprised: (a) a core containing omeprazole and an alkaline salt of omeprazole mixed with a first alkaline-reacting compound; (b) at least one intermediate layer formed by an excipient and a second alkaline-reacting compound and (c) an outer layer formed by an enteric coating. It is stated that the problem of the poor stability of the omeprazole is resolved, firstly, by increasing the way the core behaves as a base either by introducing omeprazole in the form of an alkali metal or alkaline-earth salt, or a mixture of omeprazole with a basic compound or by a combination of these two possibilities; and secondly "by incorporating an intermediate layer between the core and the enteric coating for preventing the alkaline core from causing breakdown of the enteric coating".

FR-A-2,692,146 discloses stable compositions of microgranules of gastro-protected omeprazole as well as their preparation. This documents particularly discloses a stable microgranule formulation of omeprazole comprising a neutral core consisting of sugar and starch covered with an active layer constituted by omeprazole diluted in mannitol in substantially equal amounts, and an intermediate layer comprising mannitol;an outer layer formed from an enteric coating being optionally present. There, it is indicated that the omeprazole is employed in a diluted powder form in

an amount that is substantially equal to the amount of mannitol in order to protect the omeprazole from contact with solvents and with traces of water present in the binder solutions employed for applying the mixture of omeprazole and mannitol to the neutral grains consisting of sugar and starch. Additionally, according to that patent, supplementary protection of the omeprazole applied to neutral grains is obtains by means of a second protective layer consisting of mannitol and a binder solution in order to definitively isolate the core onto which the omeprazole and the mannitol is applied. This supplementary protection isolates the omeprazole from the outer coating layer that is designed to ensure gastro-protection of the active cores.

WO96/01624 in the name of ASTRA discloses a tableted dosage form comprised of individually enteric coated layered units of a core material comprising a benzimidazole ingredient. Said individually enteric coated layered units are mixed with tablet excipients and compressed together. Said tablet excipients are e.g. microcrystalline cellulose. The resulting tablet is aid to withstand acidic environment.

SUMMARY OF THE INVENTION

The applicant has studied possible novel pharmaceutical compositions designed for oral administration of acid-labile substances, and notably omeprazole, pantoprazole, lansoprazole, leminoprazole and pariprazole, which have excellent storage stability together with stability during their preparation process, and has surprisingly found novel compositions that are particularly stable that do not include either alkaline-reacting compounds nor mannitol in a substantially stoechiometric amount, which are both stated as being essential in the prior art.

Thus, the present invention provides a composition exempt of alkaline-reacting compounds comprising:

(a)- a core containing an acid-labile benzimidazole active principle, said core being constituted of nuclei and said active ingredient mixed together and then compressed together, and said active principle not being in the form of an alkaline salt;

(b)- an intermediate layer; and

(c)- an enteric layer.

According to one embodiment, said nuclei and said active ingredient are granulated together and then compressed together.

According to one preferred embodiment, the nuclei have a particle size, in the absence of the active principle, comprised between 80 and 500 µm, preferably comprised between 150 and 300 µm.

According to a preferred embodiment, in the composition, pharmaceutical excipients, preferable at least one lubricant, are additionally present with said nuclei and said active ingredient.

According to another embodiment, at least one lubricant selected from the group comprising: sodium stearylfumarate, magnesium stearate, glyceryl behenate and talc is additionally present with said nuclei and said active ingredient.

According to another embodiment, the intermediate layer contains silicium dioxide.

Omeprazole, lansoprazole, pantoprazole, leminoprazole or pariprazole are examples of acid-labile benzimidazole active principle.

The invention also provides a method for preparing a composition according to the invention, comprising the steps of:

(i) mixing nuclei with an active principle;

(ii) compressing the product of step (i) to form a core containing an active principle;

(iii) coating said core with an intermediate layer; and

(iv) coating a product from step (iii) with an enteric layer.

According to an embodiment, step (i) is granulation.

According to another embodiment, said step (i) is carried out by spraying a medium containing an active principle onto nuclei in a fluidized bed granulator followed by drying the product thus obtained.

The medium containing the active principle is preferably an aqueous medium.

According to another embodiment, the instant process additionally comprises the step of mixing nuclei or the product of step (i) with pharmaceutical excipients, preferably with at least one lubricant.

The invention will now be described in detail with reference to the attached drawings in which:

- FIG. 1 shows the stability of the composition of example 1;

- FIG. 2 shows the stability of a prior art composition, Prilosec®.

- FIG. 3 is a photograph of granules obtained by fluidized bed granulation according to the examples.

DETAILED DESCRIPTION

Here, the expression "acid-labile substance" should be taken to mean substances the breakdown half-life of which is less than 10 minutes and/or is comprised substantially between 10 minutes and 65 hours in aqueous solutions having, respectively a pH less than 4 and/or a pH of 7. Typically, the active principles disclosed in EP 244,380 can be cited as examples, and notably omeprazole, pantoprazole, lansoprazole, leminoprazole and pariprazole.

Here, the expression "benzimidazole active principle" should be taken to mean benzimidazole derivatives that are of therapeutic value. The benzimidazole active principles disclosed in the description notably comprise omeprazole, pantoprazole, lansoprazole, leminoprazole and pariprazole together with benzimidazole derivatives described in EP 244 380, US-P-4 045 563, EP-0 005 129, BE-898 880, GB-2 141 429, EP-0 146 370, GB-2 082 580, EP-A-0 173 664, EP-A-0 080 602, EP- 0127 763, EP-0 134 400, EP-0 130 729, EP-0 150 586, DE-34 15971, GB-2 082 580, SE-A-8504048-3 and US-4 182 766. In this invention, are described preferably the compounds stated as being preferred in those documents and in particular omeprazole, pantoprazole, lansoprazole, leminoprazole and pariprazole; the alkaline salt form of the active principles cited above being excluded. Derivatives, such as salts (hydrates, etc.), esters and the like (including pro-drugs), are also contemplated, inasmuch as they are not of alkaline nature.

Mixtures of active principles are also envisaged, for example those comprising a benzimidazole in association with another active principle, or those containing two benzimidazoles.

Here, the expression "exempt of alkaline-reacting compound" should be taken to mean a composition that substantially does not contain any alkaline-reacting compound, in other words a composition in which the amount of alkaline-reacting compound is not sufficient to set up an alkaline micro-environment around the active principle when it is in contact with an acid or neutral aqueous medium, for example a micro-environment having a pH above 7.

According to this invention the core consists of a set of nuclei based on pharmaceutical-inert excipients with which the acid-labile active principle has been mixed, i.e. purely mixed, deposited, coated, aggregated, and then having been compressed together.

The expression "nuclei and active ingredient mixed together and then compressed together" covers various embodiments.

According to one embodiment, the process used for the manufacture of the instant cores is granulation, preferably fluidized bed granulation. One skilled in the art is fully aware of that technique. Elements of interest regarding said process may however be found in the publication of Schaefer & Worts, Arch. Pharm. Chemi. Sci., Ed5, 1977, 51-60. According to said granulation technique, the nuclei, e.g. lactose, are fluidized together with the inlet air, and a (binder) solution of the active ingredient is sprayed on the fluidized bed. Granules are then formed of nuclei and active ingredient; said granules are more specifically shown in figure 3. It can be seen that the solution formes a binder that holds together several nuclei; agglomeration also occurs between nuclei and/or between benzimidazole particles. Said granules, which can be considered as intermediates, are then compressed together.

Alternative embodiments may be used, e.g. where the active ingredient is present onto the nuclei, which are then compressed together, or where the active ingredient and/or

the nuclei are (partially) subject to agglomeration, and then agglomerated nuclei and/or agglomerated active ingredient and nuclei with active ingredient onto same are compressed together.

Another process that may be used for the manufacture is the tank coating technique, where the nuclei are introduced into a solution of the active ingredient, and the resulting slurry is compressed, optionally after a preliminary drying step.

Another way to express the technique for manufacturing the nuclei + active ingredient is to call it "coating technique", since a lot of possible embodiments lead to products that can be qualified as "coated products". Thus, in the instant description, the term "coating step" may be used in lieu of the term "mixing step".

In fact, on a macroscopic scale, the core may be considered as a core having dispersed therein the active ingredient.

Here, the expression "a pharmaceutically-acceptable inert excipient" should be taken to mean a compound that does not lead to a chemical reaction under operating conditions employed that can lead to breakdown of the active principle.

The nuclei can be any substance that is pharmaceutically inert vis-a-vis the active principle and can be crystalline or amorphous. These nuclei may, in general, be composed of a sugar, such as lactose, saccharose, corn starch etc. or any one of the mixtures thereof. The active principle which is optionally mixed with pharmaceutical excipients, is applied to the nuclei using any conventional coating technique employed, for example, in a suitable coating tank or in a fluidized bed device such as a granulator, with the use of suitable aqueous and/or organic solvents, or using a dry process. Coating is preferably carried out in a fluidized bed granulator. Typically Polysorbate 80 or sodium lauryl sulfate mixed with the active principle are added. Preferably, a lubricant, and notably sodium stearylfumarate or magnesium stearate or glyceryl behenate (Ompritol 888

ATO) or (micronized) talc are added after the active principle has been deposited on the inert nuclei.

Any conventional excipients used in the pharmaceutical and chemical field that are compatible with the active principle may be used, such as binders, fillers, plastifiers, surfactants, pigments, disintegrating agents, lubricants, wetting agents, etc., excepting alkaline-reacting compounds. The following can be cited as examples of excipients suitable for use in the present invention: polysorbate 80 (Tween®80), sodium lauryl sulfate, hydroxypropylcellulose, hydroxypropylmethylcellulose, talc, microcrystalline cellulose, colloidal silica, polyvinyl-pyrrolidone, sodium stearylfumarate, magnesium stearate, titanium dioxide, etc.

The intermediate layer, according to the invention consists of at least one sub-layer. It corresponds to one or several inert water-soluble layers or layers which rapidly disintegrate in an aqueous medium, containing non-acid inert pharmaceutical excipients. This layer comprises at least one polymer conventionally used in applications where a film is provided by coating such as: sugars, polyethyleneglycol, polyvinylpyrolidone, poly(vinyl alcohol), hydroxypropylcellulose, hydroxymethylcellulose, hydroxypropylmethylcellulose, etc. The intermediate layer can additionally contain any one of the conventional pharmaceutical excipients cited in the section relating to the core, or a mixture thereof, and notably silicon dioxide. This silicon dioxide is present in an amount which can vary between 2 and 45% by weight based on the dry weight of the intermediate layer, preferably 5 to 18% by weight, for example about 9%.

This intermediate layer is applied to the core using any coating technique conventionally employed in a suitable coating tank or in a fluidized bed device, with the use of suitable aqueous and/or organic solvents, or by using latex suspensions of said excipients.

The enteric layer according to this invention corresponds to a layer that is entero-soluble and gastro-resistant. It is applied to the intermediate layer by

conventional coating techniques such as coating in a tank or a fluidized bed employing polymer solutions in water or in suitable organic solvents or using latex suspensions of these polymers. As a polymer, use can be made of: cellulose acetyl phthalate, hydroxypropyl-methylcellulose phthalate, polyvinyl phthalate acetate, methacrylic acid methyl esters/methacrylic acid copolymers, such as for example, compounds known under the Eudragit®L12.5 or Eudragit®L100 (Röhm Pharma) trademarks, or similar compounds conventionally employed for the preparation of enteric coatings, as well as mixtures thereof.

The enteric coating can also be applied using aqueous dispersions of polymers, for example Aquateric® (FMC Corporation), Eudragit®L100-55 (Röhm Pharma), CE5142 coating (BASF). The enteric layer can also contain a pharmaceutically-acceptable plastifying agent such as, for example, ketanol, triacetine, citric acid esters such as those known under the Citroflex® (Pfizer) trademarks, phthalic acid esters, dibutylsuccinate or any other similar plastifying agent. The amount of plastifying agent is in general optimized for each polymer and generally represent 1 to 30% of the polymer, for example from 5 to 20%. Supplementary agents such as talc, pigments, coloring agents, flavoring agents, as well as any other excipient that conventionally enters into the composition of enteric coatings can be employed.

The compositions according to the present invention generally comprise a core representing 40 to 90% by weight, preferably 60-70% by weight based on the total weight of the composition, an intermediate layer representing 5 to 30% by weight, preferably 15 to 20% by weight, based on the total weight of the composition, and an enteric layer representing from 5 to 30% by weight, preferably 15-20% by weight based on the total weight of the composition. The core generally includes the active principle and in an amount of from 2 to 50% preferably from 5 to 20% by weight.

In one preferred embodiment, the composition according to the invention is provided in a tablet form (single, beakable, etc.).

In another prefered embodiment, the composition is in the form of micro-tablets enclosed inside a capsule, e.g. a gelatin capsule. For this, any gelatin capsule conventionally employed in the pharmaceutical formulation field can be used, such as the hard gelatin capsule known as Capsugel, available from Eli Lilly.

The compositions of this invention are particularly suitable for oral administration of the active principles and are particularly suitable for treating gastro-intestinal sicknesses.

According to one particular embodiment, the composition according to this invention takes the form of a capsule containing 16 micro-tablets, having the following composition, expressed in mg/per capsule, starting from the core and moving outwards: lactose 50 - 500, active principle 10 - 40, hydroxypropylmethylcellulose 1 - 100, Polysorbate 80 or sodium lauryl sulfate 0.0 - 5.0, sodium stearylfumarate or magnesium stearate 0.8 - 8.0, crospovidone 0-50; intermediate layer: talc 0-20, titanium dioxide 0-20, silicon dioxide 0-20, hydroxypropylmethylcellulose 3-50; enteric layer: methacrylic acid copolymer, type C 5-50, triethyl citrate 0-15, talc 0-30.

The water needed to produce each component is present in an amount of from 30 to 1000 as regards the core, 10-500 as regards of the intermediate layer and 0-1000 as regards the enteric layer. It is however also possible to use another medium, such as a medium containing water and another solvent, such as alcohol.

The invention will now be described in more detail on the basis of the following examples which are only provided by way of illustrative example.

Example 1 : Preparation of a pharmaceutical composition of omeprazole intended for oral administration.

A pharmaceutical composition according to the present invention, in the form of micro-tablets contained in a gelatin capsule having the following composition, expressed in mg, was prepared.

1 - Composition of core:

	per microtablet	per capsule (X16 tablets.)
Omeprazole	1.250	20.00
Hydroxypropylmethylcellulose	0.625	10.00
Lactose	11.875	190.00
Sodium stearylfumarate	0.150	2.40
Crospovidone	0.750	12.00
Water	7.500	120.00

2- Composition of intermediate layer

	per microtablet	per capsule (X16 tablets.)
Talc	0.375	6.00
Titanium dioxide	0.150	2.40
Hydroxypropylmethylcellulose	0.750	12.00
Water	5.000	80.00

3- Composition of the enteric layer

	per microtablet	per capsule (X16 tablets.)
methacrylic acid copolymer, type C	1.375	22.00
triethyl citrate	0.206	3.30
Talc	0.275	4.40
Water	3.750	60.00

First, the core is prepared by dissolving hydroxypropylmethylcellulose in water followed by addition of the omeprazole and homogenization of the resulting suspension. The omeprazole suspension thus obtained is sprayed onto lactose nuclei having a particle size of 250 µm, in a suitable fluidized bed granulator, such as a granulator sold by the companies Glatt, Aeromatic, etc..Any type of fluidized bed granulator conventionally used for

this type of step can be employed with the present invention. After all the suspension has been sprayed, the nuclei are dried in a conventional manner, using, for example a fluidized bed, the temperature of the product preferably remaining below 45°C. The sodium stearylfumarate and the crospovidone are than added to the dried nuclei, followed by mixing. After this, compression of the mixture obtained is carried out to obtain microtablets of a diameter of about 2.5 mm (generally comprised between 2 and 4 mm); alternatively, compression of the mixture obtained is carried out to obtain tablets of conventional dimensions. The microtablets and the tablets contain suitable amounts of the active principle.

The intermediate layer which is prepared by dissolving the hydroxypropylmethylcellulose in water followed by addition of talc and titanium dioxide followed up by homogenization, is deposited by spraying onto the microtablets. This operation can be carried out in any suitable coating device that allows a regular film to be obtained, for example a Glatt coater with a Würster type column.

The enteric layer, which is prepared by dissolving triethyl citrate in a portion of water, with addition to aqueous dispersion of methacrylic acid copolymer of type C (Eudragit L 30D-55), followed by agitation of the mixture obtained for 30 minutes and final addition of the talc suspension that was prepared in parallel by homogenizing talc in the portion of water remaining, is deposited by spraying on the tablet coated with the intermediate layer.

In order to check the stability of the microtablets prepared according to the process described above, the microtablets prepared were submitted to tests on their conservation at 45°C in the presence of 75% relative humidity. A prior art composition sold under the name Prilosec®, was also tested. This prior art composition contains agents having an alkaline reaction. The amount of omeprazole present in the microtablets at the end of the period of storage was determined by the following process:

The amount of omeprazole was determined by HPLC on a Nucleosil C18 5µ 150x4.6mm column, using for the moving phase: buffer (8.9 g Na_2HPO_4, $2H_2O$ in 1000ml of purified water; pH adjusted to 7.6 using H_3PO_4) in an amount of 73%/, acetonitrile in an amount of 27%. The detection consisted in measuring absorbency at 280nm.

The solution of the sample to be determined was prepared as follows. An accurately weighed amount of the microtablets, corresponding theoretically to about 20 mg of omeprazole was introduced into a gauged 50 ml flask. After adding the moving phase, this flask was placed in an ultrasound bath for 5 minutes. After the solution had returned to ambient temperature, the amount in the flask was adjusted to a volume of 50 ml by adding the moving phase. The concentration, Cd, in omeprazole, expressed in mg/theoretical weight of microtablets is given by the following formula:

Cd= (Aech/Aet) x(Pet/Pech) x (Vd ech/Vd et) x Pth

in which: Aech = area of peak of sample solution; Aet = area of peak of standard solution, this solution having been prepared under the same conditions as the sample solution but from a determined amount of omeprazole (20 mg); Pet = weight of the standard substance; Pech = weight of the sample; Vd ech = dilution factor of the sample; Vd et= dilution factor of the standard; Pth = theoretical weight of the test sample of microtablets (theoretically corresponding to 20 mg of omeprazole).

The results respectively obtained after 0 days, 14 days and 30 days are given in FIGS. 1 and 2 respectively for the composition according to the invention and for Prilosec®. Curves 1a and 2a represent the initial state, the respective percentages of the areas of the omeprazole peak being 99.67% and 97.51% for the composition according to the invention and, respectively, Prilosec®. Curves 1b and 2b show the situation after 14 days, the percentages then being 99.56% and 75.09% respectively. Curves 1c and 2c show the state after 30 days, the percentages then being 99.38% and 15.89% respectively.

Example 2: Preparation of a pharmaceutical composition of omeprazole intended for oral administration.

A pharmaceutical composition according to the present invention in the form of microtablets contained in a gelatin capsule having the following composition expressed in mg, was prepared

1- Composition of the core:

	per microtablets	per capsule (X16 tablets)
Omeprazole	1.250	20.00
Hydroxypropylmethylcellulose	0.625	10.00
Lactose	11.875	190.00
Magnesium stearate	0.150	2.40
Crospovidone	0.750	12.00
water	7.500	120.00

2- Composition of the intermediate layer

	per microtablets	per capsule (X16 tablets)
Talc	0.375	6.00
Titanium dioxide	0.150	2.40
Hydroxypropylmethylcellulose	0.750	12.00
Water	5.000	80.00

3- Composition of the enteric layer

	per microtablet	per capsule (X16 tablets)
methacrylic acid copolymer, type C	1.375	22.00
triethyl citrate	0.206	3.30
Talc	0.275	4.40
Water	3.750	60.00

The pharmaceutical composition was prepared according to the method described in example 1, except that the sodium stearylfumarate was replaced by magnesium stearate.

The stability of the omeprazole microtablets obtained was evaluated by the method described in example 1. The results obtained confirm those obtained for the composition according to example 1, the stability expressed as a percentage of omeprazole in the peak at 30 days being better than 99%.

Example 3: Preparation of a pharmaceutical composition of omeprazole intended for oral administration

A pharmaceutical composition according to the present invention in the form of microtablets contained in a gelatin capsule having the following composition expressed in mg, was prepared

1- Composition of the core

	per microtablet	per capsule (X17 tablets)
Omeprazole	1.176	20.0
Hydroxypropylmethylcellulose	0.588	10.0
Lactose	6.824	116.0
Sodium stearylfumarate	0.103	1.75
Crospovidone	1.603	27.25
water	6.470	110.0

2- Composition of the intermediate layer

	per microtablet	per capsule (X17 tablets)
Talc	0.294	5.00
Titanium dioxide	0.118	2.00
Hydroxypropylmethylcellulose	0.588	10.0
water	4.000	68.0

3- Composition of the enteric layer

	per microtablet	per capsule (X17 tablets)
methacrylic acid copolymer, type C	1.059	18.0
triethyl citrate	0.159	2.70
Talc	0.212	3.60
Water	4.411	75.0

The pharmaceutical composition was prepared using the method described in example 1.

The stability of the omeprazole microtablets obtained was evaluated by the method described in example 1. The results obtained confirm those obtained for the composition according to example 1.

Example 4: Preparation of a pharmaceutical composition of omeprazole intended for oral administration

A pharmaceutical composition according to the present invention in the form of microtablets contained in a gelatin capsule having the following composition expressed in mg, was prepared

1- Composition of the core:

	per microtablet	per capsule (X17 tablets)
Omeprazole	1.176	20.0
Hydroxypropylmethylcellulose	0.588	10.0
Lactose	6.824	116.0
sodium laurylsulfate	0.029	0.500
sodium stearylfumarate	0.103	1.75
Crospovidone	1.603	27.25
Water	6.470	110.0

2- Composition of the intermediate layer

	per microtablet	per capsule (X17 tablets)
Talc	0.294	5.00
Titanium dioxide	0.118	2.00
Hydroxypropylmethylcellulose	0.588	10.0
Water	4.000	68.0

3- Composition of the enteric layer

	per microtablet	per capsule (X17 tablets)
Copolymer of methacrylic acid, type C	1.059	18.0
Triethyl citrate	0.159	2.70
Talc	0.212	3.60
Water	4.411	75.0

The pharmaceutical composition was prepared using the method of example 1 except that, during the preparation of the core the sodium laurylsulfate was dissolved in water at the same time as the hydroxymethylpropylcellulose after which the omeprazole was put in suspension in this solution.

The stability of the omeprazole microtablets obtained was evaluated by the method described in example 1. The results obtained confirm those obtained for the composition of example 1.

Example 5: Preparation of a pharmaceutical composition of omeprazole intended for oral administration

A pharmaceutical composition according to the present invention in the form of microtablets contained in a gelatin capsule having the following composition expressed in mg, was prepared

1- Composition of the core:

	per microtablet	per capsule (X17 tablets)
Omeprazole	1.176	20.0
Hydroxypropylmethylcellulose	0.588	10.0
Lactose	6.824	116.0
Polysorbate 80	0.029	0.500
Sodium stearylfumarate	0.103	1.75
Crospovidone	1.603	27.25
Water	6.470	110.0

2- Composition of the intermediate layer

	per microtablet	per capsule (X17 tablets)
Talc	0.294	5.00
Titanium dioxide	0.118	2.00
Hydroxypropylmethylcellulose	0.588	10.0
Water	4.000	68.0

3- Composition of the enteric layer

	per microtablet	per capsule (X17 tablets)
Methacrylic.acid copolymer, type C	1.059	18.0
Triethyl citrate	0.159	2.70
Talc	0.212	3.60
Water	4.411	75.0

The pharmaceutical composition was prepared using the method described in example 1, except for the fact that during preparation of the core, Polysorbate 80 was dissolved in water at the same time as the hydroxymethylpropylcellulose after which the omeprazole was put in suspension in this solution.

The stability of the omeprazole microtablets (measured as in example 1) confirmed the results obtained for the composition according to example 1.

Examples 6 to 8: Preparation of pharmaceutical compositions of pantoprazole for oral administration.

The pharmaceutical compositions according to the invention in the form of individual tablets containing 40 mg of pantoprazole active principle having the following composition expressed in mg/tablet were prepared.

1- Composition of the core:

	Ex. No.6	Ex. No.7	Ex. No.8
Pantoprazole	40.00	40.00	40.00
Hydroxypropylmethylcellulose	20.00	20.00	20.00
Lactose	120.00	120.00	120.00
Polysorbate 80	-	1.00	-
Sodium laurylsulfate	-	-	1.00
Sodium stearylfumarate	1.00	1.00	1.00
Crospovidone	20.00	20.00	20.00
Water	250.0	250.0	250.0

2- Composition of the intermediate layer

	Ex. No.6	Ex. No.7	Ex. No.8
Talc	2.5	2.5	2.5
Titanium dioxide	1.0	1.0	1.0
Hydroxypropylmethylcellulose	5.0	5.0	5.0
Water	35.0	35.0	35.0

3- Composition of the enteric layer

	Ex. No.6	Ex. No.7	Ex. No.8
Methacrylic acid copolymer, type C	10.00	10.00	10.00
triethyl citrate	1.5	1.5	1.5
Talc	2.0	2.0	2.0
Water	40.0	40.0	40.0

The pharmaceutical composition was prepared using the method described in example 1, except that firstly, during preparation of the core of the compositions of examples 7 and 8, Polysorbate 80 and, respectively, sodium lauryl sulfate were dissolved in the water at the same time as the hydroxymethylpropylcellulose after which the pantoprazole was put into the suspension in the solution and, secondly, the final composition was obtained in the form of tablets, and not microtablets contained in a capsule.

The stability of the pantoprazole tablets obtained was evaluated by the method described in example 1. The results obtained confirm those obtained for the composition according to example 1.

Examples 9-11: Preparation of pharmaceutical composition of lansoprazole for oral administration.

Pharmaceutical compositions according to the present invention, in the form of microtablets contained in a gelatin capsule, having the following composition expressed in mg/capsule were prepared.

1- Composition of the core:

	Ex. No.9	Ex. No.10	Ex. No.11
lanzoprazole	30.00	30.00	30.00
Hydroxypropylmethylcellulose	15.00	15.00	15.00
Lactose	120.00	120.00	120.00
Polysorbate 80	-	0.75	-
Sodium laurylsulfate	-	-	0.75
Sodium stearylfumarate	1.25	1.25	1.25
Crospovidone	20.00	20.00	20.00
Water	200.0	200.0	200.0

2- Composition of the intermediate layer

	Ex. No.9	Ex. No.10	Ex. No.11
Talc	5.0	5.0	5.0
Titanium dioxide	2.0	2.0	2.0
Hydroxypropylmethylcellulose	10.0	10.0	10.0
Water	68.0	68.0	68.0

3- Composition of the enteric layer

	Ex. No.9	Ex. No.10	Ex. No.11
Methacrylic acid copolymer, type C	18.0	10.0	10.0
Triethyl citrate	2.7	2.7	2.7
Talc	3.6	3.6	3.6
Water	75.0	75.0	75.0

The pharmaceutical composition was prepared using the method described in example 1, except that firstly, during preparation of the core of the compositions of examples 10 and 11, Polysorbate 80 and, respectively, sodium lauryl sulfate were dissolved in the water at the same time as the

hydroxymethylpropylcellulose after which the pantoprazole was put into the suspension in the solution.

The stability of the pantoprazole tablets obtained was evaluated by the method described in example 1. The results obtained confirm those obtained for the composition according to example 1.

Example 12: Preparation of pharmaceutical composition of omeprazole for oral administration.

A pharmaceutical composition according to the present invention, in the form of microtablets contained in a gelatin capsule, having the following composition expressed in mg/ was prepared

1- Composition of the core:

	per microtablet	per capsule (X17 tablets)
Omeprazole	1.176	20.0
Hydroxypropylmethylcellulose	0.588	10.0
Lactose	6.823	116.0
Polyplasdone XL	1.603	27.25
Sodium stearylfumarate	0.103	1.75
Water	6.471	110.0

2- Composition of the intermediate layer

	per microtablet	per capsule (X17 tablets)
Talc (micronized)	0.176	3.00
Titanium dioxide	0.118	2.00
Hydroxypropylmethylcellulose	0.588	10.0
Silicon dioxide	0.088	1.50
Water	5.588	95.00

3- Composition of the enteric layer

	per microtablet	per capsule (X17 tablets)
Eudragit L 30D 55 (solid)	1.059	18.0
Triethyl citrate	0.159	2.70
Talc (micronized)	0.212	3.60
Water	4.412	75.0

The pharmaceutical composition was prepared using the method described in the examples above.

The stability of the microtablets of omeprazole (measures like in example 1) confirm the results obtained for the composition according to example 1.

Example 13: Preparation of a pharmaceutical composition of omeprazole for oral administration.

A pharmaceutical composition according to the present invention, in the form of microtablets contained in a gelatin capsule, having the following composition expressed in mg/ was prepared

1- Composition of the core:

	per microtablet	per capsule (X17 tablets)
Omeprazole	1.176	20.0
Hydroxypropylmethylcellulose	0.588	10.0
Lactose	6.823	116.0
Polyplasdone XL	1.603	27.25
Glyceryl behenate	0.103	1.75
Water	6.471	110.0

2- Composition of the intermediate layer

	per microtablet	per capsule (X17 tablets)
Talc (micronized)	0.176	3.00
Titanium dioxide	0.118	2.00
Hydroxypropylmethylcellulose	0.588	10.0
Silicon dioxide	0.088	1.50
Water	5.588	95.00

3- Composition of the enteric layer

	per microtablet	per capsule (X17 tablets)
Eudragit L 30D 55 (solid)	1.059	18.0
Triethyl citrate	0.159	2.70
Talc (micronized)	0.212	3.60
Water	4.412	75.0

The pharmaceutical composition was prepared using the process described for the examples above.

The stability of the microtablets of omeprazole (measures like in example 1) confirm the results obtained for the composition according to example 1.

Example 14: Preparation of pharmaceutical composition of omeprazole for oral administration.

A pharmaceutical composition according to the present invention, in the form of microtablets contained in a gelatin capsule, having the following composition expressed in mg/ was prepared

1- Composition of the core:

	per microtablet	per capsule (X17 tablets)
Omeprazole	1.176	20.0
Hydroxypropylmethylcellulose	0.588	10.0
Lactose	6.823	116.0
Polyplasdone XL	1.603	27.25
Talc (micronized)	0.103	1.75
Water	6.471	110.0

2- Composition of the intermediate layer

	per microtablet	per capsule (X17 tablets)
Talc (micronized)	0.176	3.00
Titanium dioxide	0.118	2.00
Hydroxypropylmethylcellulose	0.588	10.0
Silicon dioxide	0.088	1.50
Water	5.588	95.00

3- Composition of the enteric layer

	per microtablet	per capsule (X17 tablets)
Eudragit L 30D 55 (solid)	1.059	18.0
Triethyl citrate	0.159	2.70
Talc (micronized)	0.212	3.60
Water	4.412	75.0

The pharmaceutical composition was prepared using the process described for the examples above.

The stability of the microtablets of omeprazole (measures like in example 1) confirm the results obtained for the composition according to example 1.

Examples 15-17: Preparation of pharmaceutical composition of lansoprazole for oral administration.

Pharmaceutical compositions according to the present invention, in the form of microtablets contained in a gelatin capsule, having the following composition expressed in mg/capsule were prepared.

1- Composition of the core:

	Ex. No.15	Ex. No.16	Ex. No.17
lanzoprazole	30.00	30.00	30.00
Hydroxypropylmethylcellulose	15.00	15.00	15.00
Lactose	120.00	120.00	120.00
Polysorbate 80	-	0.75	-
Sodium laurylsulfate	-	-	0.75
Glyceryl behenate	1.25	1.25	1.25
Crospovidone	20.00	20.00	20.00
Water	200.0	200.0	200.0

2- Composition of the intermediate layer

	Ex. No.15	Ex. No.16	Ex. No.17
Talc	5.0	5.0	5.0
Titanium dioxide	2.0	2.0	2.0
Hydroxypropylmethylcellulose	10.0	10.0	10.0
Water	68.0	68.0	68.0

3- Composition of the enteric layer

	Ex. No.15	Ex. No.16	Ex. No.17
Methacrylic acid copolymer, type C	18.0	10.0	10.0
Triethyl citrate	2.7	2.7	2.7
Talc	3.6	3.6	3.6
Water	75.0	75.0	75.0

The pharmaceutical composition was prepared by the method described in examples 9 to 11, except that, during preparation of the core, glyceryl behenate was employed instead of sodium stearyl fumarate.

The stability of the microtablets of lansoprazole (measures like in example 1) confirm the results obtained for the composition according to example 1.

Examples 18-20: Preparation of pharmaceutical composition of lansoprazole for oral administration.

Pharmaceutical compositions according to the present invention, in the form of microtablets contained in a gelatin capsule, having the following composition expressed in mg/capsule were prepared.

1- Composition of the core:

	Ex. No.18	Ex. No.19	Ex. No.20
lanzoprazole	30.00	30.00	30.00
Hydroxypropylmethylcellulose	15.00	15.00	15.00
Lactose	120.00	120.00	120.00
Polysorbate 80	-	0.75	-
Sodium laurylsulfate	-	-	0.75
Talc (micronized)	1.25	1.25	1.25
Crospovidone	20.00	20.00	20.00
Water	200.0	200.0	200.0

2- Composition of the intermediate layer

	Ex. No.18	Ex. No.19	Ex. No.20
Talc	5.0	5.0	5.0
Titanium dioxide	2.0	2.0	2.0
Hydroxypropylmethylcellulose	10.0	10.0	10.0
Water	68.0	68.0	68.0

3- Composition of the enteric layer

	Ex. No.18	Ex. No.19	Ex. No.20
Methacrylic acid copolymer, type C	18.0	10.0	10.0
Triethyl citrate	2.7	2.7	2.7
Talc	3.6	3.6	3.6
Water	75.0	75.0	75.0

The pharmaceutical composition was prepared by the method described in examples 9 to 11, except that, during preparation of the core, micronized talc was employed instead of sodium stearyl fumarate.

The stability of the microtablets of lansoprazole (measures like in example 1) confirm the results obtained for the composition according to example 1.

Examples 21-23: Preparation of pharmaceutical compositions of pantoprazole for oral administration.

The pharmaceutical compositions according to the invention in the form of individual tablets containing 40 mg of pantoprazole active principle having the following composition expressed in mg/tablet were prepared.

1- Composition of the core:

	Ex. No.21	Ex. No.22	Ex. No.23
Pantoprazole	40.00	40.00	40.00
Hydroxypropylmethylcellulose	20.00	20.00	20.00
Lactose	120.00	120.00	120.00
Polysorbate 80	-	1.00	-
sodium laurylsulfate	-	-	1.00
Glyceryl behenate	1.00	1.00	1.00
Crospovidone	20.00	20.00	20.00
Water	250.0	250.0	250.0

2- Composition of the intermediate layer

	Ex. No.21	Ex. No.22	Ex. No.23
Talc	2.5	2.5	2.5
Titanium dioxide	1.0	1.0	1.0
Hydroxypropylmethylcellulose	5.0	5.0	5.0
Water	35.0	35.0	35.0

3- Composition of the enteric layer

	Ex. No.21	Ex. No.22	Ex. No.23
Methacrylic acid copolymer, type C	10.00	10.00	10.00
Triethyl citrate	1.5	1.5	1.5
Talc	2.0	2.0	2.0
Water	40.0	40.0	40.0

The pharmaceutical composition was prepared by the method described in examples 6 to 8, except that, during preparation of the core, glyceryl behenate was employed instead of sodium stearyl fumarate.

The stability of the microtablets of pantoprazole (measured like in example 1) confirms the results obtained for the composition according to example 1.

Examples 24-26: Preparation of pharmaceutical compositions of pantoprazole for oral administration.

The pharmaceutical compositions according to the invention in the form of individual tablets containing 40 mg of pantoprazole active principle having the following composition expressed in mg/tablet were prepared.

1- Composition of the core:

	Ex. No.24	Ex. No.25	Ex. No.26
Pantoprazole	40.00	40.00	40.00
Hydroxypropylmethylcellulose	20.00	20.00	20.00
Lactose	120.00	120.00	120.00
Polysorbate 80	-	1.00	-
Sodium laurylsulfate	-	-	1.00
Talc (micronized)	1.00	1.00	1.00
Crospovidone	20.00	20.00	20.00
Water	250.0	250.0	250.0

2- Composition of the intermediate layer

	Ex. No.24	Ex. No.25	Ex. No.26
Talc	2.5	2.5	2.5
Titanium dioxide	1.0	1.0	1.0
Hydroxypropylmethylcellulose	5.0	5.0	5.0
Water	35.0	35.0	35.0

3- Composition of the enteric layer

	Ex. No.24	Ex. No.25	Ex. No.26
Methacrylic acid copolymer, type C	10.00	10.00	10.00
Triethyl citrate	1.5	1.5	1.5
Talc	2.0	2.0	2.0
Water	40.0	40.0	40.0

The pharmaceutical composition was prepared by the method described in examples 6 to 8, except that, during preparation of the core, micronized talc was employed instead of sodium stearyl fumarate.

The stability of the microtablets of pantoprazole (measured like in example 1) confirms the results obtained for the composition according to example 1.

Comparative example.

The instant micro-tablet of example 1 are recompressed in a microcrystalline cellulose matrix using the general procedure described in the examples of WO96/01624. The resulting tablets show cracks on their surfaces, evidencing that recompression of the microtablets of the invention according to the procedure described in the WO96/01624 patent is not successful in producing suitable tablets.

Further, said final tablets have been tested as to their dissolution in a 0.1N HCl solution, according to the general procedure described in WO96/01624. Results show that after 2 hours, the dissolution is about 55%, evidencing that said final tablets cannot withstand acidic conditions.

It is clear that the particular pharmaceutical excipients described in the compositions of examples 1 to 26 can be replaced by other pharmaceutical excipients having the same function and which are conventionally employed in the pharmaceutical formulation field, provided that they are chemically compatible with the active principle.

All such alternative embodiments are covered by the scope of the invention to the extent where the stability of the resulting pharmaceutical composition is not substantially affected.

The teaching of the invention extends in fact to any of the acid-labile active principles mentioned in the introductory part of this specification, and notably those of the preferred embodiments and from the examples from the prior art. The mixing (e.g. coating, pure mixing or granulating) step of the process according to the invention can be carried out using any known technique conventionally used for this purpose. Examples which can be mentioned are coating by immersion, dry coating, dry mixing, spray coating, spray mixing, etc.

Finally, it should be noted that additional layers or sub-layers can be added, for the purposes of adding flavor and/or color, and/or improving acceptability of the medicament and/or allowing it to be marked.

WHAT IS CLAIMED IS:

1. A composition exempt of alkaline-reacting compounds comprising:
(a)- a core containing an acid-labile benzimidazole active principle, said core being constituted of nuclei and said active ingredient mixed together and then compressed together, and said active principle not being in the form of an alkaline salt;
(b)- an intermediate layer; and
(c)- an enteric layer;
omeprazole being disclaimed as a benzimidazole active ingredient.

2. The composition according to claim 1, in which said nuclei and said active ingredient are granulated together and then compressed together.

3. The composition according to claim 1 or 2, in which said nuclei have a particle size, in the absence of the active principle, comprised between 80 and 500 µm.

4. The composition according to claim 3, in which said nuclei have a particle size, in the absence of the active principle, comprised between 150 and 300 µm.

5. The composition according to any one of claims 1 to 4, in which pharmaceutical excipients, preferably at least one lubricant, are additionally present with said nuclei and said active ingredient.

6. The composition according to any one of claims 1 to 5, in which at least one lubricant selected from the group comprising: sodium stearylfumarate, magnesium stearate, glyceryl behenate and talc is additionally present with said nuclei and said active ingredient.

7. The composition according to any one of claims 1 to 6, in which the intermediate layer contains silicium dioxide.

8. The composition according to any one of claims 1 to 7, in which the acid-labile benzimidazole active principle is pantoprazole, lansoprazole, leminoprazole or pariprazole.

9. The composition according to any one of claims 1 to 8, in which the acid-labile benzimidazole active principle is pantoprazole.

10. The composition according to any one of claims 1 to 9, provided in a tablet form.

11. The composition according to any one of claims 1 to 10, provided in the form of micro-tablets enclosed inside a capsule.

12. A process for preparing a composition according to any one of claims 1 to 11, comprising the steps of:
(i) mixing nuclei with an active principle;
(ii) compressing the product of step (i) to form a core containing an active principle;
(iii) coating said core with an intermediate layer; and
(iv) coating a product from step (iii) with an enteric layer.

13. The process according to claim 12, in which step (i) is granulation.

14. The process according to claim 12 or 13, in which step (i) is carried out by spraying a medium containing an active principle onto nuclei in a fluidized bed granulator followed by drying the product thus obtained.

15. The process according to claim 14, in which the medium containing the active principle is an aqueous medium.

16. The process according to any one of claims 12 to 15, additionally comprising the step of mixing nuclei or the product of step (i) with pharmaceutical excipients, preferably with at least one lubricant.

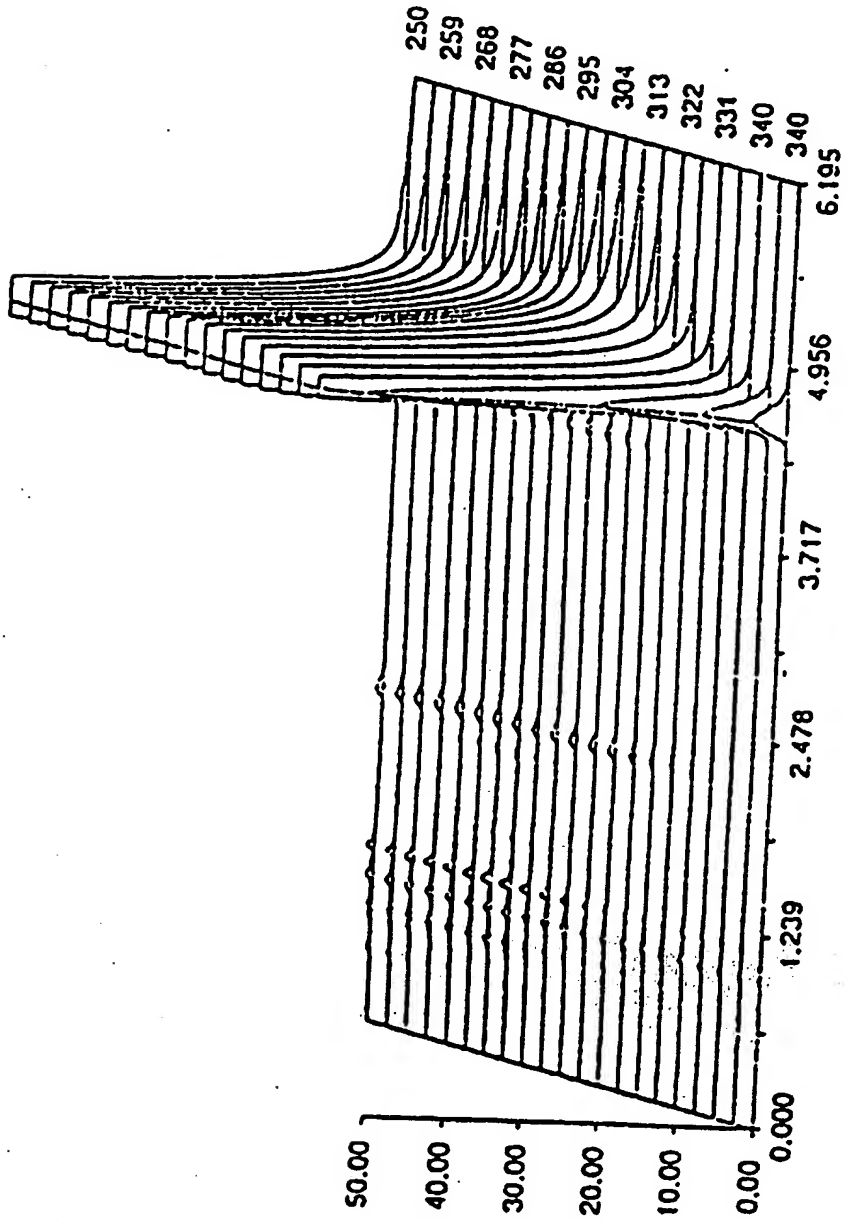
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Fig. 1a

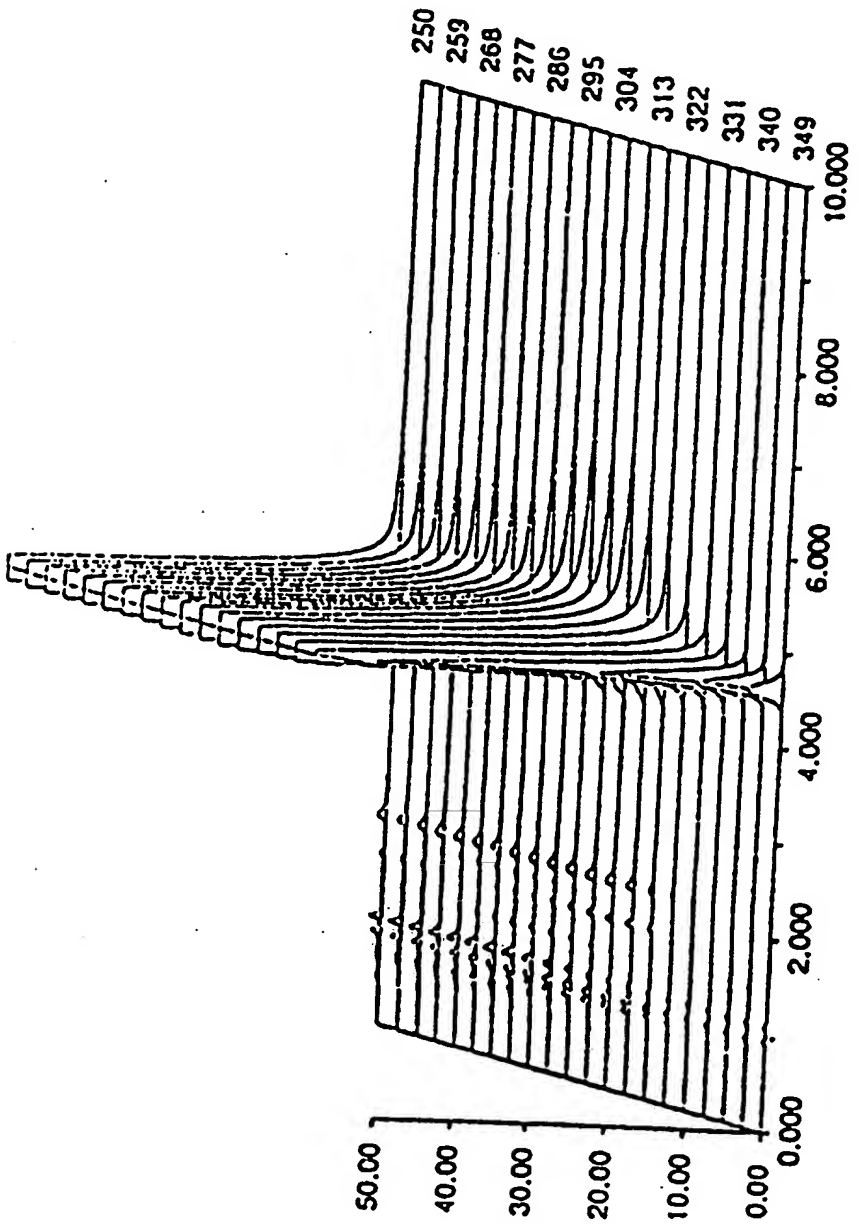
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Fig. 1b

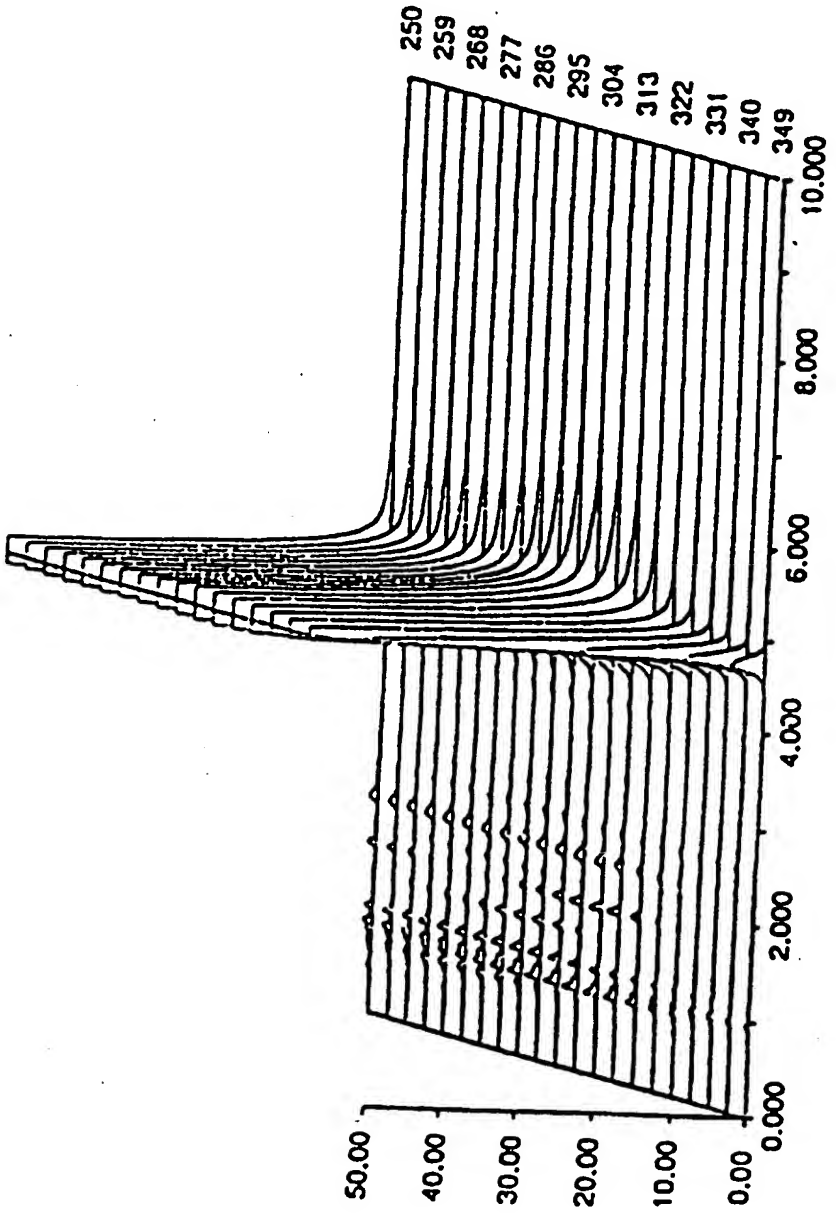
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Fig. 1c

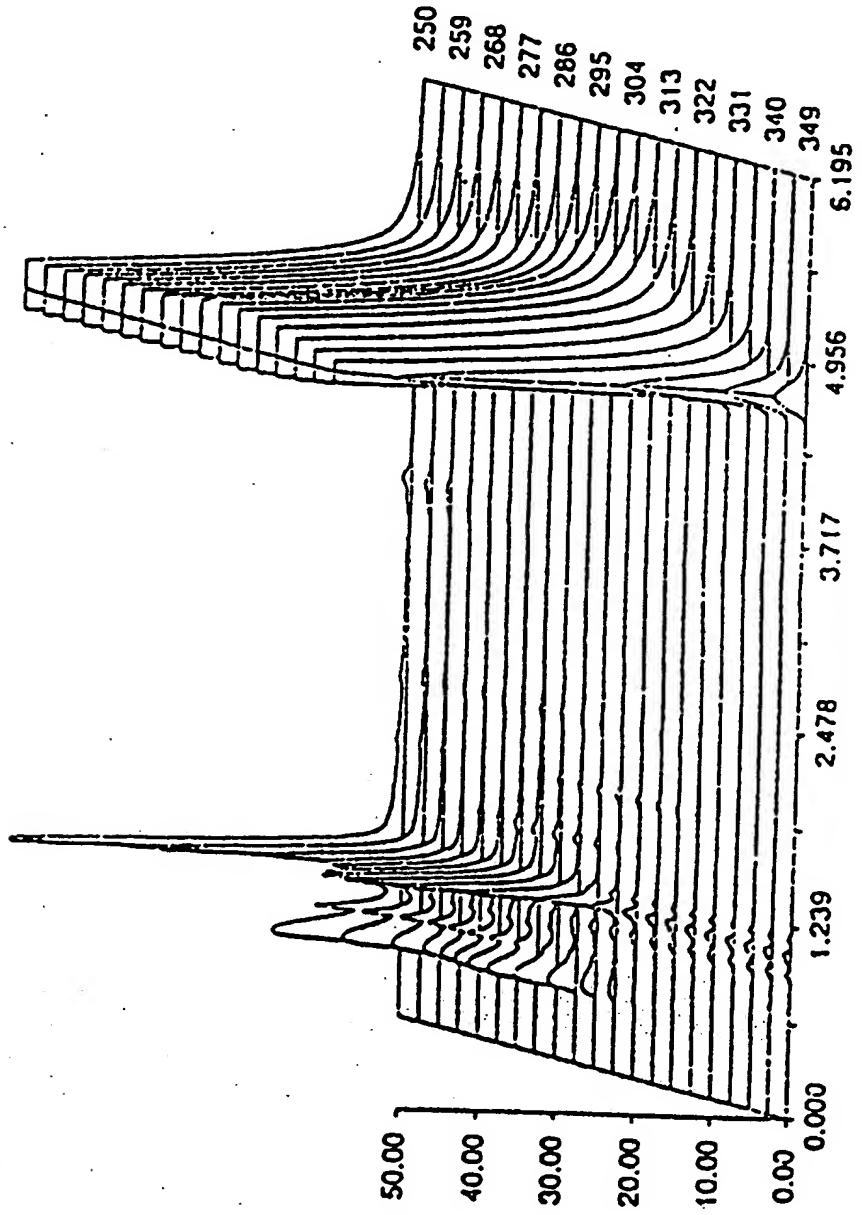
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Fig. 2a

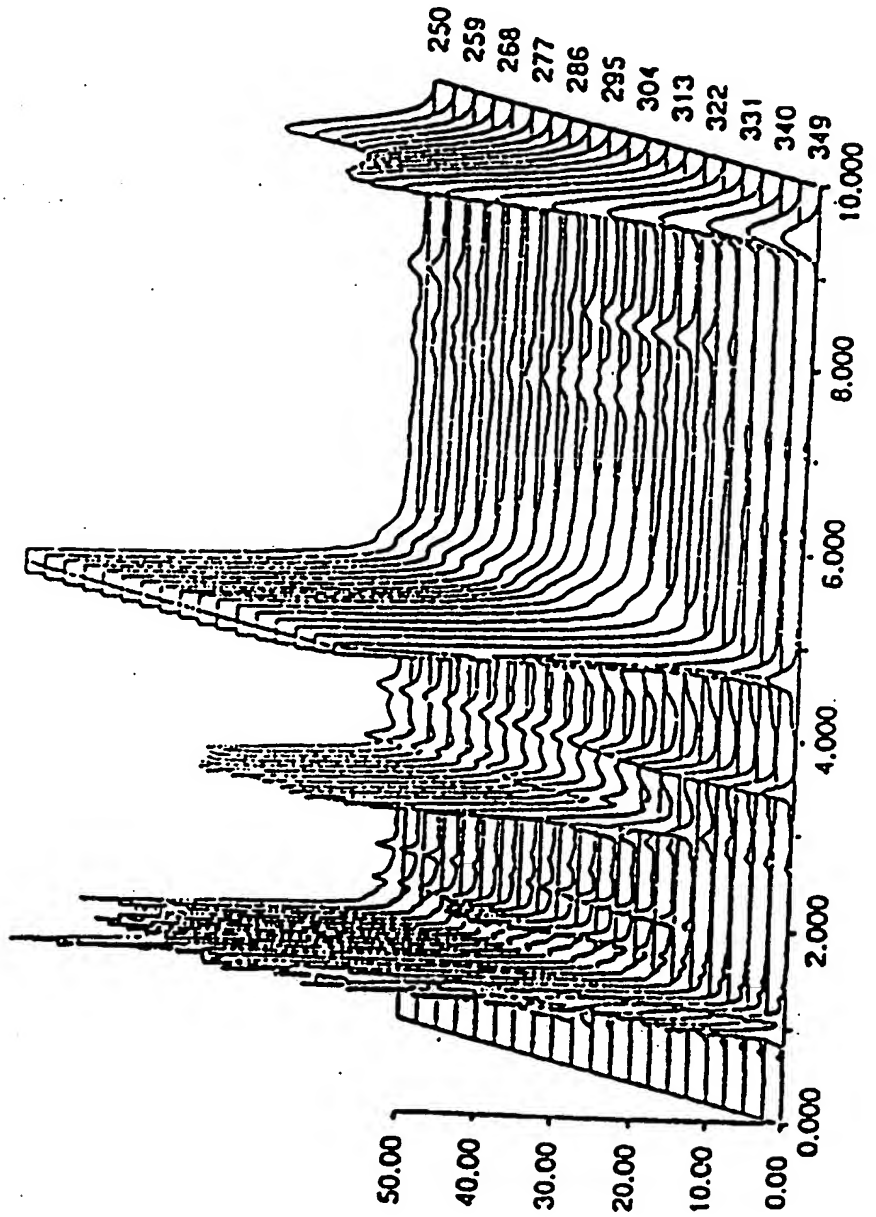
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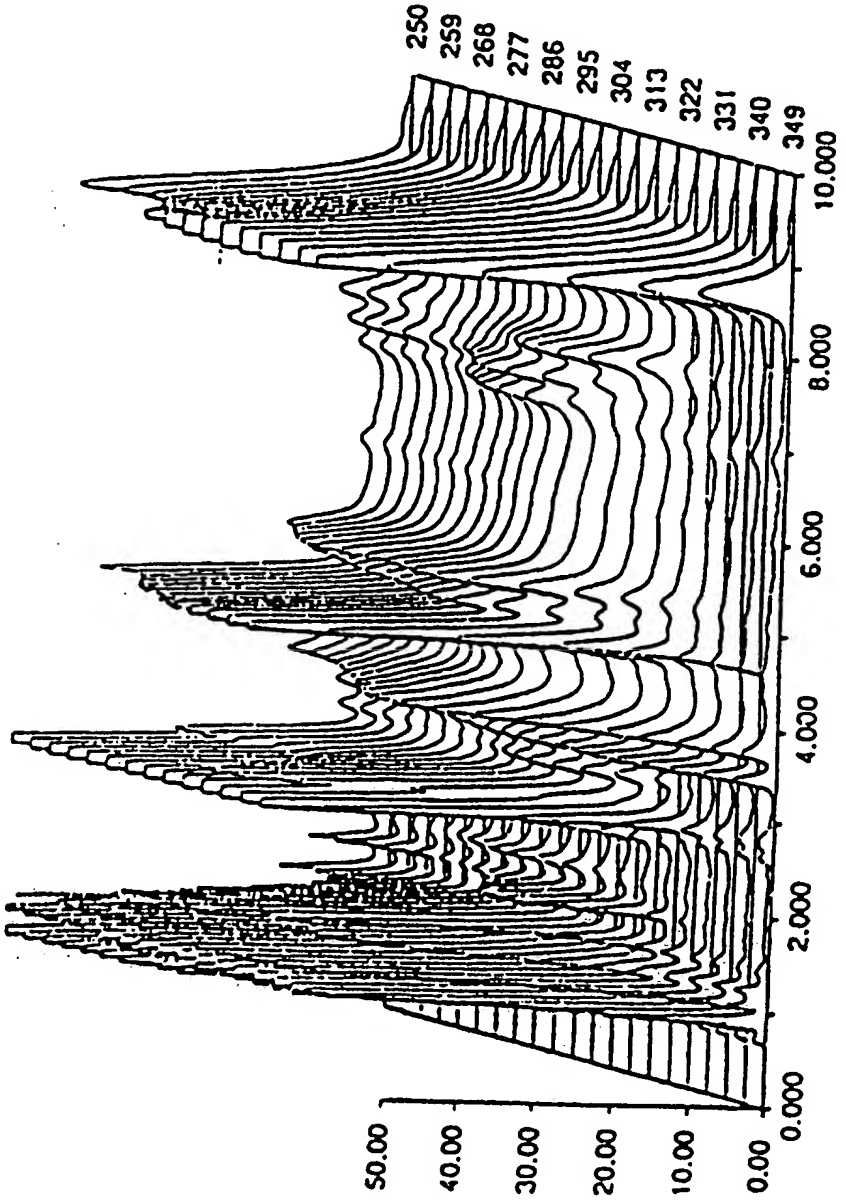
Fig. 2b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10.000
8.000
6.000
4.000
2.000
0.000
50.00
40.00
30.00
20.00
10.00
0.00

Fig. 2c

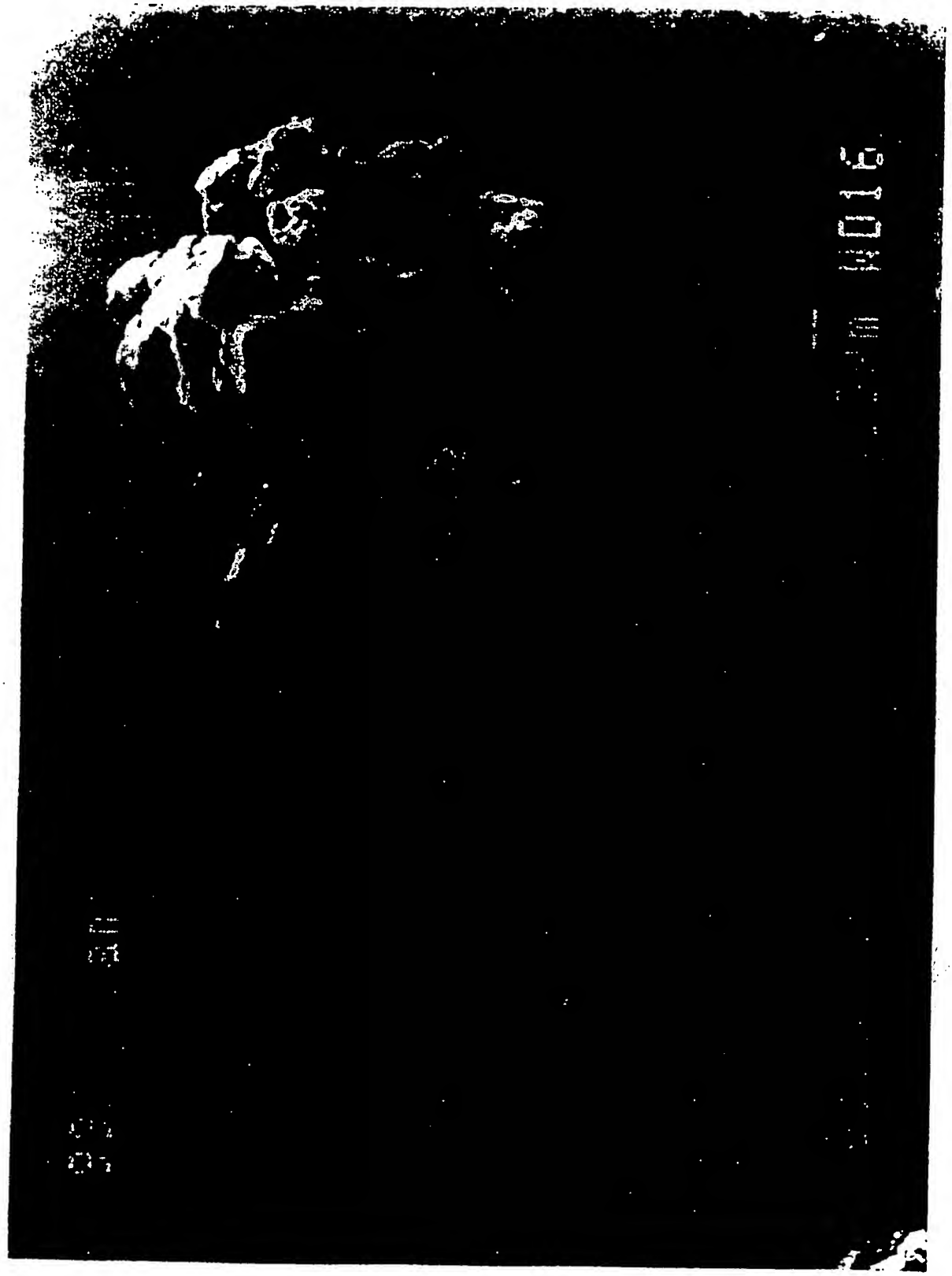

Fig. 3

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(54) **A system for enhancing the water dissolution rate and solubility of poorly soluble drugs.**

(57) Novel anhydrous compositions comprise a poorly water-soluble drug and a surfactant having enhanced dissolution rate and solubility. The drug-surfactant ratio in the composition is such that dissolution and solubility of the drug are enhanced. The compositions disclosed herein are useful in the treatment of patients (human and veterinary) as well as domestically and in agriculture.

EP 0 179 583 A1

A SYSTEM FOR ENHANCING THE WATER DISSOLUTION RATE AND SOLUBILITY OF POORLY SOLUBLE DRUGS

The invention relates to the solubilization of drugs in water. More particularly, the invention concerns the preparation of compositions comprising a poorly water-soluble drug and a surfactant by a process that enhances the water dissolution rate and solubility of the drugs by in situ micelle formation.

Many drugs, particularly poorly water-soluble or water-insoluble compounds such as ivermectin, abamectin and griseofulvin, exhibit poor, incomplete, and/or irregular absorption when administered to humans or animals because of their irregular dissolution rate. To increase dissolution rate, prior formulation systems utilized reduction in particle size by milling, by coprecipitation with a water-soluble carrier, by formation of a solid solution in a water-soluble carrier, by formation of a suitable more soluble salt, by formulation with a buffer salt, by the addition of small amounts of surfactant to improve wettability, and by adsorption onto a high-surface-area silica.

The literature contains numerous references involving processes and compositions for enhancing dissolution rate and solubility of poorly water-soluble drugs in aqueous media. Specifically, U.S. Patent Specification US-A-4,344,934 discloses compositions comprising a poorly soluble drug, a water-soluble polymer and a wetting agent that increases bio-availability of the drug. In this document polymers are used in conjunction with a wetting agent.

The use of surfactants to improve dissolution rate has been limited to reduction in the interfacial tension between the drug and dissolution media by the addition of surface-active agent to the dissolution media. The addition of surfactants improves the effective surface area of the drug by enabling the solution to wet the drug more effectively. For example, Finholt and Solvang, J. Pharm. Sci. 57: 1322 (1968) showed that the dissolution rate of phenacetin (a hydrophobic drug), was increased markedly by the addition 0.01% of polysorbate 80, a surfactant. The effect of polysorbate 80 on the rate of dissolution of the phenacetin was due only to a

small extent to its solubilizing power. It was caused mainly by its ability to decrease the interfacial tension between the substance and its dissolution medium.

Also Finholt and Solvang, Meddelelser fra Norsk, Farmacutisk Selskap, 31, 101(1969), have admixed low concentrations of surfactant with a solid drug powder or formulation, achieving the improved dissolution by a wetting phenomenon. For example, improved dissolution of phenacetin tablets resulted from dissolving polysorbate 80 in the granulating solution or spraying it as an alcoholic solution onto the dried granules.

The ability of surfactants to micellize poorly water-soluble drugs is widely known. When a surfactant is dissolved in water at very low concentrations, a fraction of it will be adsorbed at the air-water interface, and the remainder will reside in the bulk in the form of monomers. As the concentration is increased, a level is reached where the interface becomes saturated with surface-active agent and, usually simultaneously, the limiting solubility of monomer in the bulk is approached. At this concentration an unusual phenomenon occurs. Rather than precipitate, the monomers in the bulk tend to form colloidal aggregates termed micelles, which consist of 50 to 150 molecules or ions of surface-active agent. The concentration at which aggregation occurs is called the critical micelle concentration or CMC. The molecules in the micellar unit have a very definite orientation; the hydrocarbon or nonpolar portion is oriented to the centre of the micelle and is shielded from the aqueous solution. In essence a micellar solution consists of many nonpolar "droplets", which can function as a discrete phase and thereby interact with or "dissolve" drugs that would normally be insoluble in aqueous systems. This phenomenon is termed micellar solubilization. Thus, all existing literature on micellar solubilization utilizes preformed micelles in aqueous solution, i.e., the surfactant is first dissolved and then the poorly soluble drug is dissolved in the preformed micelle. The product is then stored in an aqueous medium, dispensed, and used as such.

In accordance with this invention, there is provided an anhydrous composition comprising a poorly water-soluble drug and a surfactant. The drug (e.g. ivermectin, abamectin, thiabendazole and clorsulon) is combined by suitable techniques with appropriate surfactant systems to form anhydrous products which, upon addition to water, result in solution of the

drug by in situ micelle formulation. The solubility and dissolution rate of the drug can be enhanced in accordance with the present invention.

Because of the absence of water, a concentrate suitable for dilution, without the bulk storage and handling problems associated with the equivalent more bulky aqueous system, can be obtained.

Compositions of the invention have a favourable storage mode for drugs that are susceptible to degradation in aqueous solution and simultaneously maintain the ability to obtain a clear aqueous solution upon addition to aqueous media before use.

Compositions of the invention can be administered to the human and or animal body or used in the environment, either as such or following ready dissolution into an aqueous delivery medium.

The novel compositions of the invention involve combining the poorly water-soluble drug with the surfactant in appropriate ratios and by an appropriate method that results in the formation of an anhydrous product. This product can be a solid or liquid and, on addition to water, results in a rate of solution equivalent to the surfactant and an improved water-solubility of the drug such that the composition is totally usable with water in all proportions. This process provides a formulation system that allows pharmaceutical formulation of anhydrous solid or liquid product, yet allows dissolution and solubility in water via in situ micelle formation, whereas previous micelle systems were prepared by first dissolution of the surfactant and then dissolution of the poorly water-soluble drug into the already formed micelle system.

To further decribe the novel nature of this invention and its ability to improve dissolution rate and solubility of poorly water-soluble drugs, the rate of dissolution and solubility of a poorly water-soluble drug from prior systems (Systems 1-5) are compared with the system of this invention (System 6) in Table 1.

TABLE 1

	FORMULATION	CONSEQUENCE
1)	Drug & water added	Very poor solubility and dissolution rate.
2)	Drug & (water & low concentration surfactant)	Water solubility still poor, improved dissolution rate.
3)	Drug & (water & surfactant at a concentration above the critical micelle concentration)	Improved water solubility and improved dissolution rate.
4)	(Drug & low concentration of surfactant admixed) & water	Water solubility still poor, improved dissolution rate.
5)	(Drug & physical mix of surfactant in sufficient amount to be above CMC on dilution with water) & water	Water solubility improved, improved dissolution rate. Dissolution rate will generally be less than that described in (3).
6)	(Drug & surfactant reacted as described in this application) & water	Water solubility improved. Dissolution rate faster than all other systems. Dissolution rate dependent not on the insoluble or poorly soluble drug but on the rate of solution of the water soluble surfactant selected.

The compositions of this invention (System 6 above) comprise a poorly water-soluble drug and surfactant and optionally conventional excipients and preservatives, the drug-surfactant ratio being such that a clear infinitely diluable micelle solution is formed with the addition of an aqueous medium. The compositions are prepared by one of three processes, which are generally described below:

a. Micelle/Evaporation Process

This process involves forming a traditional micelle solution with the drug and surfactant, e.g. sodium lauryl sulphate, sodium desoxycholate or Lexaine (cocoamido alkyl betaine), either by simple dissolution of both in water or by the addition of an aqueous alcoholic solution of the drug to the surfactant solution. The surfactant of choice should have a high micellization capacity and be a solid at normal room temperature. The micelle solution is then dried, e.g. by drum drying, evaporation on a Rotovac, or lyophilization. The solid obtained is an anhydrous micelle system with the drug locked in and distributed throughout the surfactant system in such a way that upon addition of water, the aqueous micelle solution is again readily obtained.

b. Solution/Adsorption Process

The poorly water-soluble drug is dissolved in a liquid surfactant such as a polysorbate, a polyoxyethylene polyol, or a sorbitan. This solution is adsorbed onto an ad-absorber such as one of those solid under the trade mark Cab-O-Sil or Accurel Powder, to form a dry flowable powder. The resulting solid anhydrous product, when placed in an aqueous medium, dissolves, forming in situ an aqueous micelle solution. An organic cosolvent or water-miscible cosolvent may be added to the surfactant to increase drug solubility in the anhydrous system.

c. Solution/Melt Process

The poorly water-soluble drug is dissolved in a molten surfactant having a melting point below that of the degradation temperature of the drug but above normal storage temperatures, e.g. a polyoxyethylene polyol, polyoxyalkylated isostearyl alcohol or ethoxylated tallowate. The solid anhydrous system, when added to an aqueous medium, will dissolve forming in situ an aqueous micelle solution.

Various active agents provide beneficial effects when administered to patients in compositions in accordance with the present invention. Such agents are exemplified by, but not limited to, the following:

(a) ß-blockers, such as propanolol, bupranolol, metoprolol, nadoxolol, sotalol, alprenolol, oxprenolol, carteolol, labetalol, atenolol, pindolol, timolol and timolol maleate.

The preferred ß-blockers are timolol, bupranolol, timolol maleate and propanolol.

(b) antimicrobial agents, such as antibacterial, antifungal and antiviral agents, e.g. lincomycin; clindamycin; tetracycline, oxytetracycline, chlorotetracycline and other tetracycline-type antibiotics; erythromycin; 2-thiopyridine N-oxide; halogen compounds, especially iodine and iodine compounds; cephalosporins, including any of the many new forms of these ß-lactam antibiotics, e.g. penicillin, penicillin G, methacillin, carbenicillin, ticaricillin, cephalosporin C, cefazolin, cephapirin, cephaloridine, cephalothin, cephanone, cefamandole, cefaparole, cefoxitin, cephacetrile, cefmetazole, cefoxitin, cefuroxime, cefotaxime, T-1551, and the oxacephalosporin S-6059; sulphonamide antibacterials; and streptomycin.

The preferred agents are linacomycin, tetracycline, erythromycin, penicillin, penicillin G, cefoxitin, streptomycin, carbenicillin, cephapirin, cephalosporin C and cephanone.

(c) steroidal anti-inflammatory agents, such as the corticosteroids hydrocortisone, hydrocortisone 17-valerate, hydrocortisone 17-butyrate, hydrocortisone 21-acetate, betamethasone valerate, triamcinolone acetonide, fluocinonide, desonide, fluocinolone acetonide, dexamethasone, dexamethasone 21-phosphate, prednisolone, prednisolone 21-phosphate, haloprednone, cortisone acetate, hydrocortisone cyclopentylpropionate, cortodoxone, flucetonide, fludrocortisone acetate, flurandrenolone acetonide, medrysone, amcinafal, amcinafide, betamethasone, betamethasone benzoate, chloroprodnisone acetate, clocortolone acetate, descinolone acetonide, desoximetasone, dichlorisone acetate, difluprednate, flucloronide, flumethasone,

flumethasone pivalate, flunisolide acetate, fluocortolone, fluorometholone, fluperolone acetate, fluprednisolone, fluprednisolone valerate, meprednisone, methyl prednisolone, paramethasone acetate, prednisolamate, prednisone, prednival, triamcinolone, triamcinolone hexacetonide, cortivazol, formocortal and nivazol.

The preferred agents are hydrocortisone, hydrocortisone 21-acetate, betamethasone, betamethasone valerate, prednisolone, prednisolone 21-phosphate, cortisone acetate, fludrocortisone acetate, triamcinolone and nivazol.

(d) Non-Steroidal anti-inflammatory agents, such as indomethacin, naproxen, fenoprofen, ibuprofen, alcolfenac, phenylbutazone, mefenamic acid, sulindac, desoxysulindac, diflunisal, aspirin, salicylamide, salicylic acid, flufenisal, salsalate, triethanolamine salicylate, aminopyrine, antipyrine, oxyphenbutazone, apazone, cintazone, flufenamic acid, clonixeril, clonixin, meclofenamic acid, flunixin, colchicine, demecolcine, allopurinol, oxypurinol, benzylamine hydrochloride, dimefadane, indoxole, intrazole, membrane hydrochloride, paranylene hydrochloride, tetrydamine, benzindopyrine hydrochloride, fluprofen, ibufenac, ketoprofen, naproxol, fenbufen, cinchophen, diflumidone sodium, fenamole, flutiazin, metazamide, letimide hydrochloride, nexeridine hydrochloride, octazamide, molinazole neocinchophen, nimazole, proxazole citrate, tesicam, tesimide, tolmetin, tramadol and triflumidate.

The preferred agents are indomethacin, naproxen, fenaprofen, sulindac, ibuprofen, diflunisal, aminopyrine, antipyrine, nimazole, tramadol, fluprofen and demecolcine.

(e) Antihypertensive agents such as clonidine and α-methyldopa, and antiangina such as propanolol hydrochloride erythrityl tetranitrate, pentaerythritol tetranitrate, isosorbide dinitrate and dioxyline phosphate; vasodilator agents such as nitroglycerin, erythritol tetranitrates, isosorbide dinitrate, mannitol hexanitrate, pentaerythrityl tetranitrate, papaverine and dipyridamole.

The preferred agents are methyldopa, clonidine and antianginas such as propanolol hydrochloride, erythrityl tetranitrate or dioxyline phosphate.

(f) Sex hormones such as estrogens, androgens and progestins, especially the natural sex hormones estradiol, testosterone and progesterone.

The preferred agents are estrogen, progestin, androgen, testosterone and progesterone.

(g) Muscle relaxants such as succinylcholine chloride, baclofen, dantrolene sodium, metaxalone, cyclobenzaprine hydrochloride and diazepan.

(h) Antiasthma agents, such as theophylline, terbutaline sulfate, dyphyline, guaifenesin and cromoglycic acid and its prodrugs [described, for example, in International Journal of Pharmaceutics, 7, 63-75 (1980)]. Because of its short half-life, cromoglycic acid is an especially desirable candidate for formulation with polyvinyl alcohol in accordance with the present invention.

(i) Antimetic agents, such as pipamazine, chlorpromazine and dimenhydrinate.

(j) Antidepressant agents, such as protriptyline hydrochloride, amitriptyline,

perphenazine and amitriptyline hydrochloride, chlordiazepoxide hydrochloride, phenizine sulfate and doxepin hydrochloride.

The preferred agents are protriptyline hydrochloride, chlordiazepoxide hydrochloride, amitriptyline and doxepin hydrochloride.

(k) Diuretics such as aldactone, diuril dyazide, enduron, hydrochlorothiazide and bretic.

The preferred agents are aldactone, diuril and hydrochlorothiazide.

(l) Vasodilator agents such as nitroglycerin, erythritol tetranitrate, isosorbide dinitrate, mannitol hexanitrate, pentaerythrityl, papaverine and dipyridamole.

The preferred agents are nitroglycerin, erythritol tetranitrate, mannitol hexanitrate and papaverine.

(m) Antiparasitic agents such as ivermectin, avermectin, abamectin, thiabendazole, milbemycin, albendazole and the like.

The preferred agents are ivermectin, abarmectin, thiabendazole, and milbemycin.

Those skilled in the art will realize that the type of beneficial agent used is not critical and that any beneficial agent can be used in accordance with the practice of this invention as long as it is soluble in the surfactant.

The surfactants useful in the practice of the invention are not critical. However, the preferred surfactants are those which result in a low surfactant to drug ratio. Representative surfactants which can be employed in the practice of the invention are polysorbates such as grades 20 and 80, polyoxyethylene polyols such as Butronic L-1, and Pluronic 25R4, sodium lauryl sulphate.

sodium desoxycholate, sorbitans such as Span 20 & 80, polyoxyalkylated isostearyl alcohols such as Arosurf^{R} grades 66-E2, E10 and E20 and the like polyoxyethylene alkyl ethers such as Brij^{R} 35, 56, and 96 and the like, polyoxyethylene polyol fatty acid esters such as Arlatone^{R} T, polyoxyethylene fatty glycerides such as Arlatone G, cocoamido alkyl betaines such as Lexaine^{R}, dioctyl sodium sulfosuccinate, ethoxylated tallowates such as Varonic^{R} LI grades 42 and 48, C-cetyl and C-decyl betaines and stearyl dimethyl benzyl ammonium chloride, ether amine salts such as Surfac^{R} grades P24M, P14B and 18-EHP and the like.

The pharmaceutical compositions containing the active ingredient may be in a form suitable for oral use, for example, as tablets, troches, lozenges, dispersible powders or granules, or hard or soft capsules. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more sweetening agents, flavouring agents, colouring agents and/or preserving agents in order to provide pharmaceutically elegant and palatable preparation.

Formulations for oral use include tablets which contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients. These excipients may be, for example, inert diluents, such as calcium carbonate, sodium chloride, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, maize starch, or alginic acid; binding agents, for example, starch,

gelatin or acacia, and lubricating agents, for example, magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules.

The pharmaceutical composition of the invention may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug, for example, cocoa butter and polyethylene glycols.

For topical use, creams, ointments, jellies, or the like containing the drug are employed according to methods recognized in the art.

Naturally, the therapeutic dosage range for the drugs employed in the practice of the invention will vary with the size and needs of the patients and the particular pain or disease symptoms being treated. However, generally speaking, the following dosage guidelines will suffice. Orally, the therapeutic dose required for a drug will range from 0.001 to 50 gram per dose preferably from 0.01 to 25 gram per dose.

The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration or use. For example, a formulation intended for oral administration of humans may contain from 5 mg to 5 g of active drug per dose compounded with an appropriate and convenient amount of carrier material which may vary from 5 to 95 percent of the total composition.

It will be understood, however, that the specific dose level for any particular patient or any other use will depend upon a variety of factors including the activity of the specific drug, the age, body weight, general health and sex of the patient, diet, time of administration, route of administration, rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

Generally, the ratio of drug to surfactant combination ranges from 1:0.05 to 1:20 (preferably from 1:1 to 1:10) by weight and the combination constitutes from 10% to 100% (preferably from 40%-98%) of the total formulation.

The following examples illustrate but do not limit various compositions of the invention and their preparation. In the Examples, mesh sizes are U.S. standards. Parts and percentages unless otherwise stated are by weight.

Micelle/Evaporation Process

EXAMPLE 1

A solution comprising 33 parts ivermectin (10 percent active) and 66 parts sodium lauryl sulphate (SLS) (100 percent active) in a 30% (v/v) aqueous methanolic solution is prepared by stirring the above in a suitable container until everything is dissolved. The solution is transferred to the receiving vessel of a Rotovap apparatus. The vessel is placed in a 40 °C water bath and sufficient vacuum applied to effect distillation of the methanol and water. The dry powder is collected and passed through a 40 mesh screen. This dry powder may be used as such or as processed in Example 10.

EXAMPLE 2

The solution of Example 1 (ivermectin, SLS and aqueous methanol) is subdivided and placed in shallow metal or glass vessels. The vessels containing the solution are placed into a commercial lyophilizer. The trays

are chilled to -30 °C or below and the vacuum of the lyophilizer is increased and the temperature permitted to rise according to the lyophilizer manufacturer's instruction until a dry powder is produced. The dry powder cake is collected and passed through a 40-mesh screen. This dry powder may be used as such or as processed as in Example 10.

EXAMPLE 3

Following the procedure of Example 2, the same product was prepared by the addition of 0.1 part disodium edetate and 0.1 part butylated hydroxytoluene to the ivermectin, SLS and aqueous methanol solution. This dry powder may be used as such or as processed in Example 10. Also, when other active agents and surfactants are substituted for the ivermectin and sodium lauryl sulphate of Examples 1 or 2, the corresponding anhydrous product is obtained.

EXAMPLE 4

Examples 1-3 are repeated with the exception that sodium desoxycholate or Lexaine P-100 is used in an appropriate drug:surfactant ratio instead of sodium lauryl sulphate. This dry powder may be used as such or as processed as in Example 10.

Solution/Ad-Absorption Process

EXAMPLE 5

A solution comprising by weight 7.5 parts ivermectin (100 percent active) in 100 parts of a non-aqueous solution comprising by volume 28.5 parts glycerol formal and 71.5 parts polysorbate 80 is prepared by stirring in a suitable container until dissolved. The solution may be used as such or as in Example 11.

EXAMPLE 6

A solution comprising by weight 7.5 parts abamectin (100 percent active) in 100 parts of a non-aqueous solution comprising by volume 36 parts glycerol formal and 64 parts polysorbate 80 is prepared by stirring in a suitable container until dissolved. The solution may be used as such or as in Example 11.

When other active agents and surfactants are substituted for ivermectin and polysorbate 80, respectively, as in Examples 5 or 6, there is obtained the corresponding product.

Solution/Melt process

EXAMPLE 7

A solution comprising by weight 7 parts ivermectin (100 percent active) in L-1 Butronic is prepared by gently heating above the Butronic melting point (approximately 45°-50°C) in a suitable container. Ivermectin is added and stirred until dissolved. The solution is allowed to cool to a waxy solid at room temperature.

EXAMPLE 8

A solution comprising by weight 7 parts ivermectin (100 percent active) in Li-42 Varonic is prepared by gently heating above the Varonic melting point (approximately 35°-45°C) in a suitable container. Ivermectin is added and stirred until dissolved. The solution is allowed to cool to a soft solid at room temperature.

EXAMPLE 9

A solution comprising by weight 7 parts ivermectin (100 percent active) in 66E20 Arosurf is prepared by gently heating above the Arosurf melting point (approximately 35°-45°C) in a suitable container. Ivermectin is added and stirred until dissolved. The solution is allowed to cool to a soft solid at room temperature.

When other active agents and surfactants are substituted for ivermectin and Butronic or Varonic, respectively, as in Examples 7-9, there is obtained the corresponding product.

Formulation Dissolution Rate

EXAMPLE 10

The powder produced in Examples 1-4 are directly compressed into tablets by conventional tableting methods. The dissolution of said tablets to yield a clear infinitely diluable aqueous solution of ivermectin is very rapid (15 minutes with gentle agitation). Compressed tablets of ivermectin alone do not dissolve or disintegrate within 3 days. The addition of a dry admixture of ivermectin and SLS to deionized distilled water resulted in dissolution rates less than those observed with the invention.

EXAMPLE 11

37 parts of each of the solutions produced in Examples 5 and 6 is dry blended with 1 part of Accurel powder (50-75% void space). This mixture is then blended with 12 parts of Cab-O-Sil to produce a dry free-flowing powder which may be used as such or tableted as in Example 10. The addition of ivermectin, alone or dissolved in glycerol formal, to an aqueous surfactant solution results in dissolution rates less than those observed with the invention.

EXAMPLE 12

The thermoplastic solids produced in Examples 7-9 are added to deionized distilled water. This mixture is stirred to affect a clear infinitely diluable solution of ivermectin. At temperatures below the melting point of the solid produced in

Examples 7-9 the rate is diminished compared to that observed when that solid is present in the molten state. This dissolution is complete at all proportions of water as shown in Example 10. The dissolution rate of ivermectin into an aqueous solution of an equivalent amount of thermoplastic surfactant is significantly slower as compared to the method of the invention.

Stability

EXAMPLE 13

A solution of 5% w/v ivermectin is prepared by dissolving the powder produced in Example 3 in sufficient deionized distilled water. This solution is stored at elevated temperature (40°C and 50°C) in a controlled environment chamber for 8 weeks. The dry powder produced in Example 3 is also stored at 25°C and 50°C. Table II presents a comparison of the stability of ivermectin in the dry state and as a micelle solution.

TABLE II

Sample	Time/ Temperature	% loss	Aqueous Composition
Solution	8 wks/40°C	16.5%	yes
	2 wks/50°C	62%	yes
Solid	12 wks/50°C	0%	no
	12 mos/25°C	0%	no

It has been demonstrated that the anhydrous in situ forming micelle powder improves the stability and storage capacity of ivermectin.

Solubility

EXAMPLE 14

A solution of 5% (50 mg/ml) w/v ivermectin is prepared by dissolving the product in Examples 1-5 and 7-9 in sufficient deionized distilled water. A mixture of an equivalent amount of ivermectin in deonized distilled water is only marginally soluble (1-4 mcg/ml). Therefore, the solubility of a poorly water soluble drug is enhanced (50,000 mcg/ml).

CLAIMS

1. An anhydrous composition comprising a poorly water-soluble drug and a surfactant.

2. A composition as claimed in Claim 1 in which the drug is a ß-blocker, antimicrobial agent, anti-inflammatory agent, non-steroidal anti-inflammatory agent, antihypertensive agent, sex hormone, muscle relaxant, antiasthma agent, antiemetic agent, antidepressant, diuretic, vasodilator or antiparasitic agent and the surfactant is a polysorbate, a polyoxyethylene polyol, sodium lauryl sulphate, sodium desoxycholate, a sorbitan, a polyoxyalkylated isostearyl alcohol, a polyoxyethylene alkyl ether, a polyoxyethylene polyol fatty acid ester, a polyoxyethylene fatty glyceride, a cocoamido alkyl betaine, a dioctyl sodium sulphosuccinate, an ethoxylated tallowate, a C-cetyl or C-decyl betaine, stearyl dimethyl benzyl ammonium chloride or an ether amine salt.

3. A composition as claimed in Claim 2 in which the drug is timolol, propanolol, bupranolol, cefoxitin, erythromycin, lincomycin, hydrocortisone, betamethasone, prednisolone, indomethacin, sulindac, diflunisal, methyldopa, clonidine, estrogen, androgen, progestin, cyclobenzaprine, baclofen, diazepan, theophyline, dyphyline, pipamazine, chlorpromazine, protriptyline, amitriptyline, aldactone, diuril, hydrochlorothiazide, ivermectin, thiabendazole, avermectin, abamectin, nitroglycerin or papaverine, and the surfactant is polysorbate 80, a polyoxyethylene polyol, sodium lauryl sulphate or sodium desoxycholate.

4. A composition as claimed in any preceding claim in which the ratio of the weight of drug to that of surfactant ranges from 1:0.05 to 1:20 and the drug-surfactant combination constitutes from 10 to 100% by weight of the total formulation.

5. A composition as claimed in Claim 4 in which the said ratio ranges from 1:1 to 1:10 and the said combination constitutes from 40 to 98% of the total formulation.

6. A composition as claimed in any preceding claim, for use in the treatment of a medical disorder.

7. The use of a composition as claimed in any one of Claims 1 to 5 in domestic or agricultural applications where the drug component is known for such use.

8. A process for preparing a composition as claimed in any one of Claims 1 to 5 comprising appropriately dissolving the drug into the surfactant at a temperature in the range from room temperature for liquid surfactants to temperatures no greater than 10 °C above the melting point of solid surfactants.

9. The process as claimed in Claim 8 including the further step of dissolving the solution obtained in an aqueous or aqueous alkanolic solvent and evaporating to a dry product at a temperature in the range -30 °C to +60 °C.

European Patent Office

EUROPEAN SEARCH REPORT

0179583
Application number

EP 85 30 7025

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int Cl.4)
X	CHEMICAL ABSTRACTS, vol. 101, no. 2, 9th July 1984, page 293, no. 12070q, Columbus, Ohio, US; N.M. SANGHAVI et al.: "Effect of various surface active agents on dissolution rate of drug phenytoin", & INDIAN DRUGS 1984, 21(5), 206-8 * Abstract *	1-9	A 61 K 47/00
X	CHEMICAL ABSTRACTS, vol. 98, no. 6, 7th February 1983, page 356, no. 40512y, Columbus, Ohio, US; N.M. SANGHAVI et al.: "Effect of surface active agents on drug dissolution of tolbutamide and phenobarbitone", & INDIAN DRUGS 1982, 19(11), 421-4 * Abstract *	1-9	
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The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	13-01-1986	BRINKMANN C.

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DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl 4)
A	DIE PHARMAZIE, vol. 37, no. 5, May 1982, pages 359-362, Berlin, DE; L.M. MORTADA: "Dissolution rates of oxyphenbutazone in surfactant solutions" * Page 359, abstract *	1-9	
D,A	EP-A-0 012 523 (AMERICAN HOME PRODUCTS) * & US - A - 4 344 934	1-9	
			TECHNICAL FIELDS SEARCHED (Int Cl 4)

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